UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/537,394	06/02/2005	Francois Romagne	INN.123	8478

23557 7590 03/26/2010

SALIWANCHIK LLOYD & SALIWANCHIK
A PROFESSIONAL ASSOCIATION
PO Box 142950
GAINESVILLE, FL 32614

EXAMINER	
SZNAIDMAN, MARCOS L	
ART UNIT	PAPER NUMBER
1612	

NOTIFICATION DATE	DELIVERY MODE
03/26/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

euspto@slspatents.com

Office Action Summary	Application No.	Applicant(s)	
	10/537,394	ROMAGNE ET AL.	
	Examiner	Art Unit	
	MARCOS SZNAIDMAN	1612	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 January 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *80-99 and 101-110* is/are pending in the application.

4a) Of the above claim(s) *89,96-99 and 103* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *80-88,90-95,101,102 and 104-110* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This office action is in response to applicant's reply filed on January 28, 2010.

Status of Claims

Amendment of claims 80, 101 and 104; cancellation of claim 100; and addition of claims 108-110 is acknowledged.

Claims 80-99 and 101-110 are currently pending and are the subject of this office action.

Claims 89, 96-99 and 103 were withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected inventions/species, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on February 19, 2008.

Claims 80-88, 90-95, 101-102, and 104-110 are presently under examination.

The following species are under examination: 3-(bromomethyl)-3-butanol-1-yl-diphosphate (BrHPP or Phosphostim) as the gamma-delta T cell activator of Formula II, and renal carcinoma as the solid tumor, which were elected in the reply filed on February 19, 2008.

Priority

The present application is a 371 of PCT/IB03/06375 filed on 10/02/2003, and claims priority to EPO 02292963.2 filed on 12/02/2002.

Rejections and/or Objections and Response to Arguments

Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated (Maintained Rejections and/or Objections) or newly applied (New Rejections and/or Objections, Necessitated by Amendment or New Rejections and/or Objections not Necessitated by Amendment). They constitute the complete set presently being applied to the instant application.

Claim Rejections - 35 USC § 112 (new Rejection Necessitated by Amendment)

> The following is a quotation of the second paragraph of 35 U.S.C. 112:
> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 80-88, 90-95, 101-102, and 104 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 80 recites" IL-2 being administered at low doses". The term "low" is a relative term which is not defined in the specification or in the claim, so it is not clear what doses are covered by the term low dose. The metes and bounds of the claim are not clearly identified.

Claim Rejections - 35 USC § 103 (New Rejection Necessitated by Amendment)

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was

not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 80-88, 90-95 and 102 are rejected under 35 U.S.C. 103(a) as being unpatentable over BioNews (http://www.investinbiotech.com/pressroom_release.php?id+644, July 8, 2002, cited in prior office action) in view of Negrier et. al. (The New England Journal of Medicine, (1998) 338:1272-1278, cited in prior office action) and in view of Espinosa et. al. (Journal of Biological Chemistry (2001) 276:18337-18344, cited in prior office action).

Claim 80, 88, 90-93 and 102 recite a method of treating renal carcinoma (species elected for a solid tumor) comprising the administration of 3-(bromomethyl)-3-butanol-1-yl-diphosphate (BrHPP or Phosphostim, species elected for the gamma-delta T cell activator) and a composition comprising interleukin-2 (IL-2) and a pharmaceutically acceptable carrier, said BrHPP and said IL-2 composition being administered separately to a subject and said BrHPP composition being administered as a single dose at the beginning of the treatment and said IL-2 being administered at low doses.

Claim interpretation: since there is no limiting definition in the specification for the term "low dose" (see 112 2nd rejection above), the term is being interpreted as broadly as is reasonable and as such is viewed as being encompassed by the prior art dosages.

For claims 80, 88, 90-93 and 102, BioNews teaches a method of treating renal carcinoma with Phosphostim (BrHPP), an activator of T gamma-delta cell (see abstract).

BioNews does not teach the administration of an IL-2 polypeptide. However, Negrier et. al. teach that IL-2 induces notable tumor regression in a limited number of patients with metastatic renal-cell carcinoma (see title and abstract).

Neither BioNews nor Negrier teach a pharmaceutically acceptable carrier. However, Espinosa teaches a composition comprising BrHPP (Phosphostim) in water (i.e. a pharmaceutically acceptable carrier, see page 18338, last three lines of the first paragraph of left column).

The statement in claim 90: "wherein BrHPP (gamma-delta T cell activator elected) is capable of inducing the proliferation of a gamma-delta T cell in a pure population of gamma-delta T cell clones when said compound is present in culture at a concentration of less than 1 mM" is an inherent property of BrHPP since the same compound should always have the same properties. MPEP 2112 I states: "[T]he discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer." *Atlas Powder Co. v. Ireco Inc.*, 190 F.3d 1342, 1347, 51 USPQ2d 1943, 1947 (Fed. Cir. 1999). Thus the claiming of a new use, new function or unknown property which is inherently present in the prior art does not necessarily

make the claim patentable. *In re Best*, 562 F.2d 1252, 1254, 195 USPQ 430, 433 (CCPA 1977).

At the time of the invention it would have been *prima facie* obvious for a person of ordinary skill in the art to treat renal cancer combining two compositions (BrHPP and IL-2) each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose. The idea of combining them flows logically from their having been individually taught in the prior art (see MPEP 2144.06). *In re Kerkhoven*, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980).

It will be further obvious to administer the composition with a pharmaceutically acceptable carrier with the motivation of better delivering the composition to the patient.

Finally, it will be further obvious to administer the two compositions separately, since dose administration is routine practice in the pharmaceutical art, thus resulting in the practice of claims 80, 88, 90-93 and 102 with a reasonable expectation of success.

Claim 81 further limits claim 80, wherein BrHPP is provided in an amount sufficient to induce at least 10-fold increase in gamma-delta T cell population in a subject.

Claim 86, further limits claim 80, wherein said gamma-delta T cell activator is provided in an amount sufficient to expand the gamma-delta T cell population in a subject to reach between 30-90% of total circulating lymphocytes in a subject.

Claim 87, further limits claim 80, wherein the biological activity of gamma-delta T cells is increased in said subject.

For claims 81 and 86-87 Espinosa further teaches that a solution of BrHPP increases the gamma-delta T cell population among total T cells in culture up to 20% at 12.5 nanomolar, 30% at 25 nanomolar and 50% at 100 nanomolar (see page 18340, Figure 4 B).

It would be further obvious to adjust the amount of Phosphostim (BrHPP) to be administered to the patient in order to increase the activity of gamma-delta T cells *in vivo*, based in the amounts disclosed by Espinosa *in vitro*, since the skilled in the art will be able to extrapolate *in vitro* data into *in vivo* data and further determine the specific amount of Phosphostim to be administered to a particular patient and adjust the dosage amounts based on the observed clinical effectiveness and the amount of increase in the gamma-delta T cell population , thus resulting in the practice of claims 881 and 86-87 with a reasonable expectation of success.

Claim 82 further limits claim 80, wherein at least two treatments are administered to subject.

Claim 83, further limits claim 80, wherein at least four treatments are administered to subject.

Claim 84, further limits claim 80, wherein BrHPP is administered in more than one treatment with an interval of about two to about eight weeks between treatments.

Claim 85, further limits claim 80, wherein BrHPP is administered in more than one treatment with an interval of about three to about four weeks between treatments.

Claim 94 further limits claim 92, wherein Phosphostim is administered in a dose to humans between 10 mg/kg to 100 mg/kg.

Claim 95 further limits claim 92, wherein Phosphostim is administered by intravenous infusion in a dose to humans that is calculated according to formula I.

For claims 82-85 and 94-95, Espinosa further teaches that a solution of BrHPP increases the gamma-delta T cell population among total T cells in culture up to 20% at 12.5 nanomolar, 30% at 25 nanomolar and 50% at 100 nanomolar (see page 18340, Figure 4 B).

BionNews in view o Negrier and Espinosa teach all the limitations of claims 82-85 and 94-95, except for the dose frequency of administration and the exact dosage. However, it's within the capability of the ordinary artisan to adjust the frequency of administration and dosage amounts based on the observed clinical effectiveness, thus resulting in the practice of claims 82-85 and 94-95 with a reasonable expectation of success.

Claim 101 further limits claim 100, wherein the IL-2 polypeptide is administered over a period of time between 1 and 10 days.

Claim 104, further limits claim 100, wherein the IL-2 is administered subcutaneously and BrHPP (Phosphostim) is administered intravenously.

Claim 105, further limits claim 104, wherein IL-2 is administered at a daily dose of between 0.2 and 2 MU per day.

Claim 106 further limits claim 104, wherein said IL-2 is administered at a daily dose between 0.2 and 1.5 MU per day.

Claim 107 further limits claim 104, wherein IL-2 is administered at a daily dose of between 0.2 and 1 MU per day.

Claim 108 further limits claim 80, wherein IL-2 is administered at a daily dose of between 0.2 and 2 MU per day.

Claim 109 further limits claim 80, wherein IL-2 is administered at a daily dose of between 0.2 and 1.5 MU per day.

Claim 110 further limits claim 80, wherein IL-2 is administered at a daily dose of between 0.2 and 1 MU per day.

For claim claims 101 and 104-110, Negrier further teaches that IL-2 was administered as a five-day continuous intravenous infusion at a dose of 18×10^6 IU (18 MU) per square meter of body surface area per day (see page 1273, under treatment, second paragraph).

Negrier does not teach the exact amounts and dose regimen disclosed in claims 101 and 104-110. However, it's within the capability of the ordinary artisan to adjust the dose regimen based on the observed clinical effectiveness, thus resulting in the practice of claims 101 and 104-110 with a reasonable expectation of success.

Response to Applicant's arguments related to the above rejection

Applicant's arguments have been fully considered but are not persuasive.

Applicant argues that:

To the extent that the examiner argues that the combination of BioNews (2002), Espinosa et al. (200t) and Negrier et al. (1998) renders the claims obvious because it would naturally follow from these references that one could treat renal cell carcinoma using the separate teachings of the references, Applicants note that IL-2 and stimulated gamma delta T-cells generate their respective e effects on renal cell carcinoma in substantially different manners. Even if these methods may both be classified as methods for treating renal cell carcinoma, the rejection does not demonstrate that one of ordinary skill in the art would regard both as useful for the same purpose and functioning in the same manner (e.g., cytokine therapy versus cell mediated cytotoxicity).

Examiner's response:

The prior art is full of examples wherein different types of diseases, and cancer in particular, have been treated with combinations of drugs that have completely different mechanism of action. The idea behind these treatments is that one mechanism of action will complement the other and will cause the maximum beneficial response from the patient. So mixing two or more drugs that are known to have the same pharmacological effect (in this case treatment of renal carcinoma), even though they might have a completely different mechanism of action (in this case: cytokine therapy and cell mediated toxicity), is routine practice in the pharmaceutical art.

Applicant argues that:

Applicants also submit that there is no evidence of record that suggests that these two diverse treatment regimens would be useful in combination for the treatment of renal cell carcinoma, particularly since Negrier et. al. indicate that none of the three tested cytokine therapies demonstrated any advantage in survival for the treated patients (see page 1277, column 2, last paragraph).

Examiner's response:

Negrier also teaches: "there is no standard treatment for metastatic renal-cell carcinoma, but many patients with this condition receive IL-2 or interferon alfa outside the setting of a therapeutic trial. These cytokines are the only drugs that have been shown to induce tumor regression in some patients. There are, however, no data to indicate which patients are most likely to benefit from such treatment and which cytokine regimen is the most active. Our results confirm that clinically relevant tumor regression occurs in a minority of cytokine-treated patients" (see page 1277, under Discussion). In other words although the IL-2 treatment is not 100% effective is still effective in treating a certain number of patients. So the skilled in the art will be motivated to further try the ad treatment of renal cancer patients with IL-2 or combinations of IL-2 an other drugs that have already been proved to be effective for the treatment of renal carcinoma.

Applicant argues that:

Even assuming that this is the case, Applicants further submit that there is no rationale provided as to why one skilled in the art would have been motivated to use low dose IL-2 for the treatment of renal cell carcinoma. In this respect, Negrier et al. teach the use of 18 x 106 IU (18 MU) of IL-2 for the treatment of renal cell carcinoma. Other than the assertion made in the Office Action, no reasoning is provided as to why one skilled in the art would have been motivated to use low dose IL-2 therapy (e.g., ranging from 0.2-2 MU IL-2) for the treatment of renal cell carcinoma. As the Supreme Court stated, "*there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness*." *KSR Int'l v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007) (quoting In re Kahn, 441 F.3d 977, 988 (Fed. Cir. 2006) (emphasis added)). In this case, no such articulated reasoning is provided (other than the argument that "it is within the capability of the ordinary artisan to adjust the dose regimen based on the observed clinical effectiveness"; Office Action at page 10). Applicants submit that the ordinary artisan would not have been motivated to use IL-2 doses that are between 9 and 90 times lower than that taught in Negrier et al.

Examiner's response:

The amounts that Negrier discloses are for monotherapy treatment of renal cancer. When combining IL-2 with another drug that is effective for the treatment of renal cancer, the skilled in the art will be able to modify the amount taught by Negrier in order to adjust it for the effect of the other drug has on the treatment of renal cancer.

The amount of each drug that is being administered will be adjusted based on the maximization efficacy and the minimization of side effects, all of which is routine practice in the pharmaceutical art.

Withdrawn Rejections and/or Objections

Claims rejected under 35 USC 103 (a)

Due to Applicant amendments of the claims the 103(a) rejection is withdrawn.

However, based on new considerations a new 103(a) rejection is applied (see above).

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any

extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MARCOS SZNAIDMAN whose telephone number is (571)270-3498. The examiner can normally be reached on Monday through Thursday 8 AM to 6 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Frederick F. Krass can be reached on 571 272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/MARCOS SZNAIDMAN/
Examiner, Art Unit 1612
March 23, 2010.

/Frederick Krass/
Supervisory Patent Examiner, Art Unit 1612